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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/029,579	05/06/98	LANDEGREN	U 1209-122P

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EXAMINER

GANSHEROFF, L

ART UNIT PAPER NUMBER

1636

*16*

DATE MAILED:

12/05/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

## Office Action Summary

Application No.

09/029,579

Applicant(s)

LANDEGREN, ULF

Examiner

Lisa J. Gansheroff

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☐ Responsive to communication(s) filed on \_\_\_\_.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-7 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-7 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_ is/are objected to.
- 8) ☐ Claims \_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_ is/are objected to by the Examiner.
- 11) ☐ The proposed drawing correction filed on \_\_\_\_ is: a) ☐ approved b) ☐ disapproved.
- 12) ☐ The oath or declaration is objected to by the Examiner.

### Priority under 35 U.S.C. § 119

- 13) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
- a) ☒ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_.
  - ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

### Attachment(s)

- 15) ☒ Notice of References Cited (PTO-892)
- 16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) \_\_\_\_.
- 18) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_.
- 19) ☐ Notice of Informal Patent Application (PTO-152)
- 20) ☒ Other: *Notice to Comply with Sequence Rules*.

### **DETAILED ACTION**

Pending claims: 1-7

The request filed on 3 November, 2000 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/029579 is acceptable and a CPA has been established. An action on the CPA follows.

#### ***Oath/Declaration***

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because: the filing date for the application should be 6 May, 1998. The Oath indicates 6 March, 1998.

#### ***Specification***

This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b).

An abstract on a separate sheet is required.

#### ***Information Disclosure Statement***

The single document on the IDS filed previously with 09/029579 (Nilsson et al., 1994), has been considered in the examination of this CPA.

*Sequence compliance*

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

For example, there is an oligonucleotide sequence on page 7. All sequences in the specification must be listed in the Sequence Listing and must comply with the requirements of 37 CFR 1.821 - 1.825. In addition to providing a Sequence Listing in paper and computer readable form with the requisite statement that the two are the same and contain no new matter, the specification should also be amended to identify the sequence with a SEQ ID NO: in the text, in accordance with the Requirements.

Any response to this Office Action which fails to meet all of these requirements will be considered non-responsive. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a). Direct the reply to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the reply.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

This rejection was made in the previous office actions and is retained for the reasons of record.

Briefly:

The following factors have been considered in determining that the specification does not enable the skilled artisan to make and use the invention.

**The nature of the invention.** The invention is drawn to a pharmaceutical composition. By the word “pharmaceutical”, the scope of the claim is clearly meant to encompass a composition to be used *in vivo* to have a pharmaceutical effect. The claim also recites that the padlock probe oligonucleotide is capable of direct inhibition of transcription, and the scope of the claim would include transcription *in vivo*. Thus, the invention is complex.

**The state of the prior art and the predictability or unpredictability of the art.** The examiner did not find, and the applicants did not point to any prior art that discloses the use of the exact structure of the padlock probe oligonucleotides of the invention as part of pharmaceutical compositions with predictable treatment effects. Thus, any pharmaceutical effects of the padlock probe oligonucleotides could not be assumed to be predictable based on the prior art. In related art, at the time of the invention of the instant application the use of

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pharmaceutical oligonucleotide formulations was unpredictable. As noted in the previous office action, the use of antisense oligonucleotides and other molecules meant to target specific nucleic acid sequences to cause an *in vivo* effect was very unpredictable. The article cited in previous office action which excerpted a discussion at an antisense conference in May of 1997 (Nature Biotechnology, Vol. 15, pages 519-525) reviews the unpredictability of the field at the time of the instant invention. In that article, James Wyngaarden commented on a meeting that had occurred in New Orleans two years prior to the 1997 meeting, "I came away from the New Orleans meeting with a feeling that more people were skeptical than were believers that antisense was going to work" (page 519). It is noted that the instant application is a 371 filing of a PCT application filed September, 1996, and that it claims priority to a foreign application filed in 1995. Thus, as noted in the previous office action, the art of oligonucleotides as pharmaceuticals was unpredictable. It was unpredictable at the priority date of the instant application, and it remained unpredictable years later, as evidenced by the references of record cited in the previous office actions. For example, in the Nature Biotechnology article, Arthur Krieg stated "reproducibility of finding has been a problem" (page 522), and page 522 also discusses the difficulties in extrapolating between results *in vitro*, meaning in cells in culture, and *in vivo*, meaning in animal. In another reference cited in a previous office action, Branch (1998, TIBS 23:45-50) reviews the unpredictability of the antisense art, including for example the fact that nucleic acid drugs have been found to act on molecules other than the intended target, and that these effects are unpredictable.

**The amount of direction or guidance presented in the specification and the presence or absence of working examples.** The Applicants present an example of a padlock probe

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oligonucleotide binding to double stranded DNA in a highly defined biochemical system in Example 1 (noted in a prior office action as *in vitro* biochemistry/enzymology). In Example 2, Applicants show that a padlock probe oligonucleotide inhibits transcription in a highly defined system similar to that of Example 1, but it is unclear whether the padlock probe inhibits transcription of double-stranded DNA, since the specification states that the padlock probe "was allowed to hybridize to a denatured, amplified fragment". As noted in previous office actions, no guidance is provided with regard to using the padlock probe oligonucleotide pharmaceutically. Applicants do not even present any examples of the padlock probe having an effect in a cell, where the DNA is not purified but is in chromatin, in the nucleus, with many other cellular components around, such as nucleases. The previous office actions noted issues related to uptake of oligonucleotide composition by cells and avoiding nuclease activity. Applicants also do not present teachings demonstrating pharmaceutical effects of compositions comprising padlock probe oligonucleotides.

**The breadth of the claims.** The claims are very broad, as they are drawn to pharmaceutical compositions and thus are drawn to effects not only in a test tube but also in animals.

**The quantity of experimentation.** Based on the lack of working examples and guidance from the specification and the prior art relating to pharmaceutical compositions comprising the padlock oligonucleotide probes, and based on the unpredictability of related pharmaceutical oligonucleotide art, an undue amount of experimentation would be required for one of skill in the art to make and use the claimed pharmaceutical composition.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 7 is rejected under 35 U.S.C. 102(b) as being anticipated by Nilsson et al. (1994), for the reasons of record. Claim 7 is drawn to a composition comprising an effective amount of a padlock probe oligonucleotide.

Nilsson et al. teach a padlock probe that meets the structural limitations of the claims and targets single-stranded nucleic acid. As recited in the previous office action, although the instant claim recites an intended use of targeting double-stranded nucleic acid, a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. See *In re Casey*, 152 USPQ 235 (CCPA 1967) and *In re Otto*, 136 USPQ 458, 459 (CCPA 1963). In further support of this rejection, Applicants are referred to the MPEP section 2112. For example, in 2112.01 the MPEP states that a “chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present.”



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All claims are drawn to the same invention claimed in the parent application prior to the filing of this Continued Prosecution Application under 37 CFR 1.53(d) and could have been finally rejected on the grounds and art of record in the next Office action. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing under 37 CFR 1.53(d). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lisa J. Gansheroff whose telephone number is (703) 605-1203. The examiner can normally be reached 9 AM - 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Richard Schwartz can be reached at (703) 308-1133. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242 for regular communications.

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Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the patent analyst Dianiece Jacobs whose telephone number is (703) 305-3388 or to the receptionist whose telephone number is (703) 308-0196.

LG

November 29, 2000



REMY YUCEL, PH.D  
PRIMARY EXAMINER